Exhibit 4

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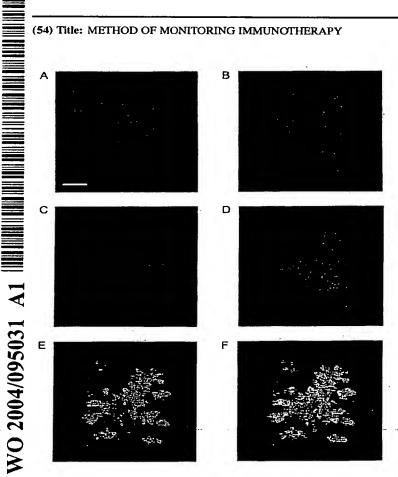
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[Continued on next page]

(54) Title: METHOD OF MONITORING IMMUNOTHERAPY



(57) Abstract: The present invention relates to a method of monitoring an immunotherapy against amyloidosis and other diseases characterized by the deposition of abnormal protein aggregates. More specifically, it relates to a method of evaluating an immunotherapy against Alzheimer's disease, based on a novel assay that is characterized by scoring immunoreactivity levels of patient sera in amyloid plaque containing samples. The assay possesses highly predictive properties in relation to the clinical outcome of such an immunotherapy, in contrast to previously used, conventional ELISA assays. Therefore, the novel assay is useful for the evaluation of the efficacy of an immunotherapy in a patient suffering from amyloidosis, particularly Alzheimer's disease.

> Applicants: U.S. Serial No.: Filed:

Christoph Hock et al. 10/554,314 October 15, 2003

Exhibit 4

INTERNATIONAL SEARCH REPORT

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A. CLASS IPC 7	G01N33/68								
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Documenta	tion searched other than minimum documentation to the extent that	such documents are included in the fields s	earched						
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)									
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C. DOCUM	ENTS CONSIDERED TO BE RELEVANT								
Category °	Citation of document, with indication, where appropriate, of the re	levant passages	Relevant to claim No.						
X	US 5 164 295 A (KISILEVSKY ROBER 17 November 1992 (1992-11-17) abstract; claims 1,4	T ET AL)	11-15						
X	DU Y ET AL: "Reduced levels of a beta-peptide antibody in Alzheima disease" NEUROLOGY, vol. 57, no. 5, 11 September 2001 (2001-09-11), p 801-805, XP009026218 ISSN: 0028-3878 abstract page 804, right-hand column, para 2,3; table 1	er [*] Dages	1-10						
Y Furth	er documents are listed in the continuation of box C.	W Delay tamba and barren							
<u> </u>		X Patent family members are listed	ui cullica.						
Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filling date "L" document which may throw doubts on priority claim(e) or "It document which may throw doubts on priority claim(e) or "It document which may throw doubts on priority claim(e) or "It document which may throw doubts on priority claim(e) or									
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Name and m	aling address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Weijland, A							

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Internation Application No
PCT/EP 03/11413

		PCT/EP 03/11413			
(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT					
egory *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
	DODEL RICHARD ET AL: "Human antibodies against amyloid beta peptide: A potential treatment for Alzheimer's disease" ANNALS OF NEUROLOGY, vol. 52, no. 2, August 2002 (2002-08), pages 253-256, XP009026281 ISSN: 0364-5134 abstract page 1	1-10			
	WO 95 20979 A (CERAMI ANTHONY ;ULRICH PETER C (US); VITEK MICHAEL P (US); VLASSAR) 10 August 1995 (1995-08-10) the whole document	1-15			
	WO 01 40261 A (ORTHO MCNEIL PHARM INC) 7 June 2001 (2001-06-07) the whole document	1-15			
	EP 1 172 378 A (DODEL RICHARD DR; YANSHENG DR DU (US)) 16 January 2002 (2002-01-16) abstract; figure 1 column 4, line 53 - line 58 column 5, line 1 - line 13	1-16			
	WO 02 46222 A (BUCK MARTINA ; CHOJKIER MARIO (US)) 13 June 2002 (2002-06-13) the whole document				
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internation pplication No
PCT/EP 03/11413

Patent document cited in search report			Publication date		Patent family member(s)	Publication date
US	5164295	Α	17-11-1992	NONE		
WO	9520979	Α	10-08-1995	AU	692237 B2	04-06-1998
				AU	1870195 A	21-08-1995
				CA	2182731 A1	10-08-1995
				EP	0802797 A1	29-10-1997
				JP	9511492 T	18-11-1997
				WO	9520979 A1	10-08-1995
				US	6410598 B1	25-06-2002
			20.	US	5935927 A	10-08-1999
WO	0140261	Α	07-06-2001	AU	1920401 A	12-06-2001
				CA	2393004 A1	07-06-2001
				EP	1233979 A1	28-08-2002
				JP	2003530542 T	14-10-2003
				WO	0140261 A1	07-06-2001
EP	1172378	Α	16-01-2002	EP	1172378 A1	16-01-2002
				US	2002009445 A1	24-01-2002
WO	0246222	Α	13-06-2002	US	2002137112 A1	26-09-2002
				AU	1982402 A	18-06-2002
				EP	1339743 A2	03-09-2003
				WO	0246222 A2	13-06-2002
				US	2003104488 A1	05-06-2003